REMARKS/ARGUMENTS

This Response and Amendment responds to the Office Action dated November 17, 2003, and the Advisory Action dated December 24, 2003. It is the Applicant's understanding from the Advisory Action that the prior filed Response and Amendment dated November 24, 2003 was not entered. Therefore, this Response and Amendment assumes that the claim set pending in the present application prior to this Response and Amendment is the claim set pending at the time of the November 17, 2003 Office Action.

The Applicant notes that the Advisory Action indicates on page 2, under 'continuation of 5,' that the "proposed amendment to Claims 57-59, 61-65 and 81 was not entered for the reasons set forth above in "2." As there are no Claims 57-59, 61-65 and 81 in the present application, the Applicant assume that this comment was in error and will not respond to it.

Claims 11-16, 18, 19, 21-24 and 28-34 are pending in the present application. Claims 11-16, 18-19 and 28 stand rejected. Claims 21-24 and 29-34 are withdrawn from consideration. In response, claims 29-34 have been canceled, claims 11 and 18 have been amended to replace the word "material" with the word "matrix," and previously canceled claims 20 and 25-27 have been rewritten as new claims 35-38. Support for these amendments is given below. No new matter is added by these amendments. Entry of these amendments is requested.

With Respect to the Withdrawal of Claims 21-24 and 29-34, Paragraphs 3-5 of the Office Action:

Claims 21-24 stand withdrawn as being drawn to a nonelected species and claims 29-34 stand withdrawn as being drawn to a nonelected invention. Claims 29-34 are canceled by this amendment.

With respect to claims 21-24, as indicated below, claims 11-16, 18-19 and 28 are now believed to be in condition for allowance. As stated in the Office Action dated March 7, 2003, Paper No. 6, paragraph 9, claims 21-24 were withdrawn from further consideration as being drawn to a nonelected species as there was no allowable generic or linking claim. As claims

21-24 depend upon claim 11, and claim 11 is now believed to be in condition for allowance for the reasons indicated below, rejoinder of claims 21-24 is hereby requested.

With Respect to the Rejections Under 35 U.S.C. § 102 and 103, Paragraphs 8-11 of the Office Action:

Claims 11-16, 18, 19, and 28 are rejected under 35 U.S.C. § 102(e) and under 35 U.S.C. § 103(a) for the reasons indicated in paragraphs 8-10 of the Office Action, and for the reasons indicated on page 2 of the Advisory Action. In the Advisory Action, the Patent and Trademark Office stated that:

> The proposed amendment of claim 11 does not overcome the prior art of Stimpson [United States Patent 6,037,186] because Stimpson does disclosed [sp] stabilizing the bundle in a matrix (col. 4, line 28; col. 10, lines 16-34). Additionally, the definition of matrix in the specification (pg. 5, lines 22-26), would encompassed [sp] the "matrix" of Stimpson (col. 9, lines 31-36).

The Applicant respectfully traverses the rejections and the above reasoning. The Applicant believes that the Patent and Trademark Office has erroneously confused disclosure in the '186 Patent directed to putting binding agents, which correspond to the target substances of the present invention, in a matrix, with embedding the bundle of target-strands made of the binding agents/target substances in a matrix. This confusion can be understood by reviewing the present application, the '186 Patent and the reasoning cited by the United States Patent and Trademark Office as follows.

The three passages of the '186 Patent cited by the United States Patent and Trademark Office in the Advisory Action as support for the refusal to enter the prior Response and Amendment are in total as follows:

> The **array elements can be subjected to a quality control step** before assembly into the bundle used to make the arrays. [col. 4, lines 27-29, with line 28 in bold]
>
> ...generated by cutting slabs. The mechanics of combinatorial synthesis using a flat sheets or rods of material are the same as those described by U.S. Pat. No. 5,175,209 with the flat sheets or rod elements replacing the porous wafers as the substrates for synthesis. The book format can attain reasonable spatial densities by using thin sheet

materials, e.g., track etch polyester or polycarbonate membranes are only 10 microns thick so that 1000 pages combine to give a book only 1 cm thick.

The sheet or rod materials must be compatible with the reagents used during organic synthesis. Typically glass particles or cross-linked polystyrene particles are used in standard DNA synthesis with phosphoramidite chemistry and the solvents acetonitrile, dichloromethane, and tetrahydrofuran are present. Hence, a likely candidate for the present invention is Empore.RTM., a sheet of chemically bonded silica particles suspended in a web of polytetrafluoroethylene (PTFE) microfibrils, i.e., both the silica and PTFE are resistant to the chemicals used in DNA synthesis... [col. 10, lines 16-34]

Nitrocellulose has a natural affinity for proteinaceous materials like antibodies and the material can **be directly applied and immobilized by adsorption. For DNA, a number of commercially available membrane products exist for covalent linkage. For example, Immobilon (Millipore), or Biodyne C (Pall Biosupport, Glencove, N.Y.) have been used for covalent immobilization of small nucleic acids (10-20 bases) via an** amino group added during synthesis. (col. 9, line 29-37, with lines 31-36 in bold)

None of the passages above cited by the United States Patent and Trademark Office appear to define the term "matrix" as used in the '186 Patent. The term "matrix" referred to in the '186 Patent appears to be most clearly defined in several other passages, however. For example:

> In one embodiment, the **elements of the array are formed by the ends of rods of porous materials** which are compatible with a chemical synthesis or compound application step. For application of proteinaceous (e.g. antibodies) or nucleic acid (e.g. derived from a cDNA library) compounds **the porous matrix** can be selected from any of the materials currently used to produce microporous membranes by a phase inversion or a leaching process. [col. 3, lines 47-54, emphasis added]
>
> Printing a line of binding agent on the porous sheet results in migration of the agent into the matrix of the material. [col. 5, lines 18-20]
>
> Ink printed on the surface of porous sheets results in some migration of the ink into the matrix of the sheet. [col. 7, lines 54-56]
>
> The main requirement of the porous material used for immobilization is that it allow some of the binding agent to penetrate into the matrix, i.e., more than pure surface

> deposition. In addition, since **the matrix of the material forms the binding zones of the array** a substantially uniform membrane is desired. For this reason, membranes with a highly asymmetric structure or which contain embedded fabrics are less desirable for the present invention than uniform membranes. [col. 9, lines 31-39, emphasis added]
>
> In cases where flow through the array is needed to improve sensitivity, the porous rod or sheet materials must have a pore size sufficiently large to allow entry of the label into the matrix, otherwise the label reaction is confined to the rod surface. [col. 12, lines 5-8]

From the above cited passages, it is clear that the term "matrix" as used in the '186 Patent refers to the substance where the 'binding agents' are initially embedded to form 'elements of the array' or 'binding zones of the array.'

The 'binding agents' in the '186 Patent correspond to the "target substances" of the present invention, and the'elements of the array' or 'binding zones of the array' correspond to the "target-strands" of the present invention. This relationship can be appreciated from the following passages of the '186 Patent, among many others:

> Finally, in the area of in vitro diagnostics there is a need for panel assays where several tests are run concurrently on a given sample using an array of immobilized binding agents. [col. 1, lines 52-55]
>
> If each element (i.e. a zone of immobilized binding agent) was a square only 1 millimeter (1 mm=0.1 cm) in size, an array of 65536 elements would be 10 inches on a side. [col. 2, lines 13-16]
>
> The object of the present invention is to extend array construction into a third dimension, Z, so that each array element formed by a synthesis or application of a binding agent is used to produce many arrays. Individual arrays are formed by cutting slabs along the Z axis of a bundle assembled from the various array elements. [col. 3, lines 30-35]
>
> Each rod is dipped or otherwise exposed to a unique binding agent to allow uniform attachment throughout its length (Z axis). [col. 4, lines 5-7]

Claims 11 and 18 have been amended to replace the word "material" with the word "matrix." The passage of the present application cited by the Patent and Trademark Office as

support for the refusal to enter the prior Response and Amendment was page 5, lines 22-26 which defined "matrix" as used to embed target substances. The term "matrix" in the present application, however, is also disclosed in connection with one method of embedding the bundle of target-strands, including in the passage immediately prior to the passage cited by the Patent and Trademark Office.

This passage was previously cited in support of the amended claims in the non-entered Response and Amendment, the same amendments to claim 11 and 18 being made in this Response and Amendment, along with other passages as follows (noting that the passage cited by the Patent and Trademark Office was not among those listed for support by the Applicant) (emphasis added):

> Stabilizing the Bundle of Target-Strands
>
> The method of producing high density arrays according to the present invention can also include a step of **stabilizing the bundle of target-strands.** Stabilization can improve the form or the function of the bundle or array, such as making the bundle easier to section, or isolating target substances from each other in the array. The stabilizing step can be performed at any time during or after the assembly of the bundle of target-strands, as is appropriate to the type of stabilization. For example, **stabilization can be accomplished by embedding the bundle of target-strands in a matrix**, such as epoxy, polypropylene or polystyrene. [page 8, lines 9-16]
>
> The fiber are then assembled into bundles with the location of each fiber and its associated immobilized target substance noted in the database. **The bundle of fibers is preferably stabilized by embedding or otherwise impregnating the bundle in a matrix to provide structural support to the bundle.** [page 9, lines 21-24]
>
> If necessary, **the bundle is stabilized such as by embedding or otherwise impregnating the bundle in a matrix to provide structural support to the bundle.** [page 10, line 27 to page 11, line 1]
>
> Referring now to Figures 6 to 8, there are shown respectively, a plurality of membranes 28 having lines of target substances 30 applied on each membranes 28; **the membranes 28 stacked and stabilized to form the bundle 32;** and the bundle 32 being sectioned to produce a plurality of

high density arrays 34, where each array has target substances 28 arranged in two analytical axes.

Referring now to Figures 9 to 11, there are shown respectively, a membrane 36 having lines of known target substances 38 applied on membrane 36; **the membrane 36 being rolled and stabilized to form a bundle 40;** and the bundle 40 being sectioned to produce a plurality of high density arrays 42, where each array has target substances 38 arranged in two analytical axis. [page 11, lines 10-19]

The bundle of tubes is preferably stabilized by embedding the bundle in a matrix to provide structural support to the bundle. [page 12, lines 7-8]

The bundle of threads is stabilized by embedding it in a matrix such as polymethacrylate, epoxy resins, polyethylene glycol, paraffin waxes, gums, poly acrylamide and other similar materials which can, preferably, be handled in liquid form at elevated temperature or in unpolymerized form suitable for embedding the threads. The embedded threads are allowed to harden or to crosslink to impart a rigid structure to the bundle. [page 14, lines 3-8]

The stabilized bundle is then sectioned perpendicular to the long axis of the threads using a microtome or similar device to create a plurality of high density arrays preferably having a thickness of between about 0.1 and 100 microns. Each resultant high density array has the same pattern of DNA sequences in specific spatial regions or zones of the array with the target substances arranged in two analytical axis. [page 14, lines 15-19]

The term "bundle" as used in the present application is disclosed at page 6, lines 2-6, as follows:

> As used herein, the term "bundle" refers to an ordered arrangement or assembly of target-strands. For example, a bundle can include a stack of target-strands where each target-strand comprises a tube filled with a target substance, or where each target-strand comprises lines of target substances drawn on a membrane, or where each target-strand comprises a wire of a target substance.

In contrast to the explicit teaching of the present application, above, and as claimed in currently amended claim 11, that is to section a bundle of target-strands that has been stabilized by embedding the bundle in a matrix as presently claimed, the entire disclosure of the '186 Patent appears to be limited to creating arrays using radial compression to form a bundle, and then cutting the bundle formed by radial compression. For example, the following passages disclose the reliance on radial compression to form the bundle (emphasis added):

> When all array elements are available they are formed into a rod bundle using radial compression about the Z axis of the bundle. The rods may be organized in the bundle by using a guide, i.e., a plate with a series of holes to direct the rods to a particular point of the array. The bundle can be compressed by pulling it through a cone shaped guide. **A sheath is wrapped around the bundle, as in the insulation around a bundle of conducting electrical wires, to hold the elements in place.** The resulting rod bundle is then sliced into multiple arrays along the Z axis. [col. 4, lines 22-31]
>
> The spools are fed into the guide and pulled through to form a rod bundle with the appropriate go spatial arrangement of rod elements. **A sheath is applied to the rod bundle as it emerges from the guide** and the bundle is either wrapped on a new larger spool or cut into convenient lengths for storage or directly cut into slab arrays. [col. 4, lines 57-63]
>
> FIG. 2D shows an end view of an array cut from the roll of FIG. 2C after rolling is complete and **the structure is bound with a sheath 260**. The array is a spiral structure of multiple layers of sheet material 210 separated by interstitial spaces 250 and wrapped about a core cylinder 240. [col. 6, line 64 through col. 7, line 1]
>
> After reagent application, the membrane is rolled around a rod shaped support to form a tight spiral of membrane material similar to a "jelly roll". **The outer surface is bound with a material that supplies radial compression (e.g. heat shrink insulation or adhesive tape)** and the resulting roll is cut into individual arrays along the Z axis. In this case, the arrays are spiral in nature with each array element formed by the freshly cut edge of the sheet material impregnated with the various binding agents. **The support rod can be a hollow tube or a solid cylinder.** When a pressure sensitive adhesive is used for the sheath, a few layers of untreated sheet are wrapped on the outside of the spiral to

prevent direct contact between the tape and array elements. In this way, the array elements are protected from adhesive migration during cutting. [col. 7, line 66 through col. 8, line 13]

In summary, the invention is directed toward the detection of components in a sample mixture or detection of compounds on an array by:

a) immobilizing binding compounds onto rod shaped array elements;

b) forming a bundle of the rod elements using a guide to create a spatially uniform arrangement of rod elements and **securing with a sheath material**; [col. 12, lines 57-64]

b) rolling the printed sheet into spiral wound structure about a rod and **securing roll with a sheath;** [col. 13, lines 23-24]

c) forming a bundle of the rod elements and **securing with a sheath material**; [col. 13, lines 43-44]

b) forming a bundle of the rod elements and **securing with a sheath material** so that rod elements treated with a given binding agent are grouped to create a graphic symbol/s surrounded by rod elements with different or substantially no affinity for components in the test sample; [col. 13, lines 54-59]

After printing, the sheet was rolled tightly by hand around a plastic straw, and bound with adhesive tape....

The arrays were surprisingly stable and easily handled even though **the layers of the spiral are only held in place by compression** between the central rod (straw) and the outer sheath (adhesive tape). [col. 14, line 50 through col. 15, line 2]

The membrane was rolled, bound and cut into slab arrays and placed on a paper towel. [col. 16, lines 22-23]

b. forming a bundle of compounds in a generally elongated form by collecting the sheet containing the immobilized compounds about a common axis to form an elongated bundle and **wrapping the sheet in a spiral**; and [claim 1; col. 16, lines 43-47]

b. rolling the impregnated sheet into a spiral wound structure about a rod and **securing the structure with a sheath** to form a bundle; [claim 10, col. 17, lines 15-17]

The '186 Patent does disclose the use of an adhesive, such as for example (emphasis added):

> **In some cases it may be desirable to use an adhesive compound to bind either the sheets in a stack or the layers of a rolled sheet together to form a cohesive structure.** The adhesive used for this purpose must not migrate during the cutting process used to form the individual arrays or else the edges of the sheet material become covered with adhesive and are not accessible to test solutions. Suitable adhesives for binding the sheets are heat activated-double sided Dow Adhesive Films (Dow Chemical, Midland, Mich.). The important features of adhesive selection are: (1) the adhesive does not wet and thereby occlude the pores of the sheet material before and during setting (2) the adhesive sets to a substantially solid consistency that does not migrate and cover the sheet edges during cutting (3) the set adhesive is not brittle and susceptible to cracking when the individual arrays are released from the bundle or roll and (4) the adhesive is stable to the aqueous solvent of the test sample. In general, pressure sensitive adhesives (e.g. Scotch Tape.RTM., 3M, St. Paul, Minn.) are not desirable because of adhesive migration during mechanical cutting. However, other cutting methods using lasers may allow the use of pressure applied adhesives. One advantage of the roll format over the stack format is that, typically, the compressional forces supplied by the sheath in the rolled structure are sufficient to maintain the integrity of the individual arrays cut from the roll without using any adhesive. This is true for both rod bundles and spiral sheet bundles. [col. 5, line 48 through col. 6, line 7]

However, it appears clear the "adhesive" is not used to embed the bundles, because of the requirement for radial compression, discussed above, which would be unnecessary if the bundles were embedded, because of the specific disclosure regarding the "adhesive" cited below, and because the '186 Patent discloses the existence of "intervening spaces," "interstitial space" and "pores" between the array elements.

> The invention is based on the observation that arrays cut from bundles of porous rods or spiral wound porous sheets behave like membranes

composed of said porous materials and conduct flow through the multitude of edges exposed during cutting. Surprisingly, liquid flows substantially through the multiple porous rod or sheets which comprise the array and **not through the intervening spaces between the array elements**. [col. 3, lines 38-46]

FIG. 2C is a schematic view of the process where by the reagent impregnated sheet 200 is rolled about a cylindrical support 240 to form a spiral wound structure of multiple layers **separated by an interstitial space 250 between said layers**.

FIG. 2D shows an end view of an array cut from the roll of FIG. 2C after rolling is complete and the structure is bound with a sheath 260. The array is a spiral structure of multiple layers of sheet material 210 **separated by interstitial spaces 250** and wrapped about a core cylinder 240. [col. 6, line 59 through col. 7, line 1]

In some cases it may be desirable to use an adhesive compound to bind either the sheets in a stack or the layers of a rolled sheet together to form a cohesive structure. The adhesive used for this purpose must not migrate during the cutting process used to form the individual arrays or else the edges of the sheet material become covered with adhesive and are not accessible to test solutions. Suitable adhesives for binding the sheets are heat activated-double sided Dow Adhesive Films (Dow Chemical, Midland, Mich.). The important features of adhesive selection are: (1) **the adhesive does not wet and thereby occlude the pores of the sheet material before and during setting** (2) the adhesive sets to a substantially solid consistency that does not migrate and cover the sheet edges during cutting (3) the set adhesive is not brittle and susceptible to cracking when the individual arrays are released from the bundle or roll and (4) the adhesive is stable to the aqueous solvent of the test sample. In general, pressure sensitive adhesives (e.g. Scotch Tape.RTM., 3M, St. Paul, Minn.) are not desirable because of adhesive migration during mechanical cutting. However, other cutting methods using lasers may allow the use of pressure applied adhesives. One advantage of the roll format over the stack format is that, typically, the compressional forces supplied by the sheath in the rolled structure are sufficient to maintain the integrity of the individual arrays cut from the roll without using any adhesive. This is true for both rod bundles and spiral sheet bundles. [col. 5, line 48 through col. 6, line 7]

> c) cutting individual arrays from the bundle to expose binding elements formed by the freshly exposed edge of sheet material separated by identification marks and **interstitial space between adjacent membrane layers**, and fixing or placing one side of the array onto an absorbent pad; [col 13, lines 25-30]

Accordingly, the '186 Patent does not teach or suggest the limitation of claim 11 of "sectioning a bundle of target-strands that has been stabilized by embedding the bundle in a matrix." All other pending claims depend on claim 11. Therefore, withdrawal of the rejections under 35 U.S.C. § 102(e) and 103(a) and allowance of claims 11-16, 18, 19 and 28 is hereby requested.

With Respect to Previously Canceled Claims 20 and 25-27:

Claims 35-38 are added by this amendment and are identical to previously canceled claims 20 and 25-27 which were canceled on December 10, 2002 in response to a restriction requirement. These claims have been placed back into the application and a request for reconsideration of these claims is hereby requested as generic claim 11, on which claims 35-38 depend, is now believed to be in condition for allowance. If, however, the United States Patent and Trademark Office still considers claims 35-38 not to be allowable even in view of their dependency upon claim 11, the Applicant authorizes the United States Patent and Trademark Office to cancel new claims 35-38 by Examiner's Amendment without further argument.

CONCLUSION

Claims 11-16, 18-19 and 28 are now believed to be in condition for allowance for the reasons stated above and a Notice of Allowance is earnestly solicited. Additionally, the Applicant requests reconsideration of the withdrawal of claims 21-24 and consideration of claims 35-38. If, however, there remain any issues that can be resolved by telephone with the Applicants representative, the Examiner is encouraged to contact the undersigned directly.

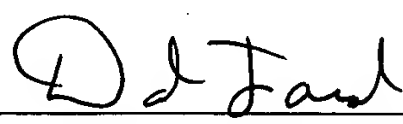
If any extension of time is required, such extension is hereby requested. No fee is believed due in connection with this communication. However, if any fee is due, the

Commissioner is hereby authorized to charge payment of the fee associated with this communication to Deposit Account No. 19-2090.

Respectfully submitted,

SHELDON & MAK PC

Date: February 2, 2004

By: 
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